Associations between neuropsychiatric and health status outcomes in individuals with probable mTBI

Jessica Bomyea[a,b*], Laura A. Flashman[c], Ross Zafonte[d], Norberto Andaluz[e], Raul Coimbra[b], Mark S. George[fg], Gerald A. Grant[h], Christine E. Marx[ij], Thomas W. McAllister[ck], Lori Shutter[e], Ariel J. Lang[a,b], Murray B. Stein[bm]

a. VA San Diego Healthcare System Center of Excellence for Stress and Mental Health; La Jolla, CA, US

b. University of California, San Diego Department of Psychiatry; La Jolla, CA, US

c. Dartmouth Geisel School of Medicine at Dartmouth, Dartmouth-Hitchcock Medical Center, Department of Psychiatry; Hanover, NH, US

d. Spaulding Rehabilitation Hospital, Massachusetts General Hospital, Brigham and Womens Hospital, Harvard Medical School, Department of Physical Medicine and Rehabilitation; Boston, MA, US

e. University of Cincinnati, Gardner Neuroscience Institute; Cincinnati, OH, US

f. Ralph H. Johnson VA Medical Center, Psychiatry Division; Charleston, SC, US

g. The Medical University of South Carolina, Department of Psychiatry and Behavioral Sciences; Charleston, SC, US

h. Stanford University Medical Center, Department of Neurology and Neurosciences; Stanford, CA, US

i. Durham VA Medical Center, Durham, NC, US

j. Duke University, Department of Psychiatry and Behavioral Sciences; Durham, NC, US

k. Indiana University School of Medicine, Department of Psychiatry; Indianapolis, IN, US

l. University of Pittsburgh, Department of Critical Care Medicine, Neurology, and Neurosurgery; Pittsburgh, PA, US

This is the author's manuscript of the article published in final edited form as:
Bomyea, J., Flashman, L. A., Zafonte, R., Andaluz, N., Coimbra, R., George, M. S., … Stein, M. B. (2018). Associations between neuropsychiatric and health status outcomes in individuals with probable mTBI. Psychiatry Research. https://doi.org/10.1016/j.psychres.2018.12.021

m. University of California, San Diego Department of Family Medicine and Public Health; La Jolla, CA, US

***Corresponding author: jbomyea@ucsd.edu**

Keywords: traumatic brain injury, disability, functioning, quality of life, neuropsychology, memory, posttraumatic stress disorder

Abstract

Mild traumatic brain injury (mTBI) is a common occurrence, and may impact distal outcomes in a subgroup of individuals. Improved characterization of health outcomes and identification of factors associated with poor outcomes is needed to better understand the impact of mTBI, particularly in those with co-occurring posttraumatic stress disorder (PTSD). Participants in a data repository of the Injury and Traumatic Stress (INTRuST) Clinical Consortium (*N*=625) completed functional disability [FD] and health-related quality of life [HRQOL] questionnaires, and a subset completed a neuropsychological assessment. FD and HRQOL were compared among participants with probable mTBI (mTBI), probable mTBI with PTSD (mTBI/PTSD), and health comparison participants (HC). Associations between symptoms, neuropsychological performance, and health outcomes were examined in those with probable mTBI with and without PTSD (*n*=316). Individuals in the mTBI/PTSD group endorsed poorer health outcomes than those in the mTBI group, who endorsed poorer outcomes than those in the HC group. Individuals in either mTBI group performed worse than those in the HC on verbal learning and memory and psychomotor speed. Health outcomes were correlated with mental health and postconcussive symptoms, as well as neuropsychological variables. mTBI may adversely impact self-reported health, with the greatest effect observed in individuals with co-occurring mTBI/PTSD.

1. Introduction

Traumatic brain injury (TBI) occurs when a force to the head (e.g., blunt injury, blast) causes alteration of consciousness (AOC) or loss of consciousness (LOC), posttraumatic amnesia, neurological deficits, and/or intracranial lesion (Bryant et al., 2010). TBI is highly prevalent, with the Centers for Disease Control and Prevention estimating approximately 1.7 million cases per year (Faul, 2010). Mild TBI (mTBI), which is the most typical variant of TBI, is defined by the American College of Rehabilitation Medicine (ACRM) as an injury associated with LOC for less than 30 minutes, less than 24 hours of posttraumatic amnesia, and a Glasgow Coma Scale rating of 13-15 (Bazarian et al., 2005). mTBI exposure can be associated with a host of physical (e.g. headache), cognitive, and mental health (e.g., depression, PTSD) sequelae. Typically symptoms resolve naturally over a short timeframe (McRory et al., 2013), but a subgroup of individuals report emotional, cognitive, or functional symptoms following the acute recovery phase (Boyle et al., 2014; O'Neil et al., 2017; Stein et al., 2016; Vasterling et al., 2017). For example, Jak and colleagues found in a sample of 411 veterans with a history of probable mTBI that average mental health symptom scores fell in the clinical range and 28% demonstrated impaired neuropsychological performance on two or more tests (Jak et al., 2015), while McMahon and colleagues found that 22.6% of civilian individuals with mild TBI reported functional and postconcussive symptoms one year post-injury (McMahon et al., 2014). The etiology of chronic symptoms may be attributable to non-concussive factors (e.g., pre-existing or new onset psychiatric disorders (Donnell et al., 2012; Lagarde et al., 2014)) and remains a controversial topic (for reviews see (Broshek et al., 2015; Hoge et al., 2009; Silverberg and Iverson, 2011)). Irrespective of the source of chronic symptoms, improved characterization of global health outcomes in this group, as well as identification of factors associated with poor health outcomes, is needed to better understand the broad impact of mTBI.

Two commonly used metrics to assess health status outcomes include functional disability (FD) and health-related quality of life (HRQOL). FD refers to the impact of a particular disease state on one's

ability to conduct activities of daily living, including work or social functioning. FD reflects an evaluation of the burden of a particular condition (Nichol et al., 2011). Though precise definitions of HRQOL are not universally agreed upon, the World Health Organization considers HRQOL to be the individual's "perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (Kuyken et al., 1995). Thus, although HRQOL is similar to FD in its assessment of the extent of a problem's impact, it can be conceptualized as a subjective or contextualized report of the experience relative to the individual's ideal (Nichol et al., 2011).

mTBI has been associated with higher levels of FD (Scholten et al., 2015; Whiteneck et al., 2016) and lower ratings of HRQOL in individuals with a history of mTBI as compared to healthy comparison participants (Ahman et al., 2013; Beseoglu et al., 2013; Dijkers, 2004; Emanuelson et al., 2003). A recent review by Polinder and colleagues (Polinder et al., 2015) noted a substantial degree of variability in functional outcomes within individuals with TBI, highlighting the need to examine predictors of HRQOL within this group of individuals (see also (Petchprapai and Winkelman, 2007)). Although diminished FD and HRQOL have been found in studies of mTBI, clinical variables that are associated with FD and HRQOL in mTBI have been understudied to date.

FD and HRQOL outcomes following mTBI likely depend on multiple external (e.g., environment) and internal factors, including mental health variables (Kay, 1992). Jackson and colleagues recently reported that veterans with mTBI and PTSD, but not veterans with mTBI only, differed from healthy comparison participants on a measure of psychosocial functioning (Jackson et al., 2016), suggesting that psychiatric symptoms are a primary contributor to health outcomes. Although data on non-military samples is limited, a study by Haagsma and colleagues reported associations between higher self-reported PTSD symptoms and worse HRQOL and FD in a civilian mTBI sample (Haagsma, 2015). Postconcussive symptoms (PCS) might also contribute to poor perceived health status. PCS include a

constellation of cognitive, sensory, emotional, and physical complaints that the individual reports as beginning after head injury. PCS are associated with ratings of FD and HRQOL in individuals with mTBI (Emanuelson et al., 2003; Schiehser et al., 2015). However, their high overlap with mental health symptoms (Belanger et al., 2010) and non-specific nature (Cassidy et al., 2014) raises the possibility that psychological distress, rather than mTBI-specific problems, is the etiological factor linking them to lower health ratings. To date, studies examining FD and HRQOL have not reported separately on psychiatric symptoms and postconcussive symptoms when examining the relationship of each to subjective ratings of health outcomes.

Neuropsychological factors may also be associated with ratings of FD and HRQOL in individuals with mTBI, yet this possibility has been understudied. Extant literature is mixed with regard to neuropsychological impairments observed in mTBI. Some studies suggest those with mTBI demonstrate modest performance reductions in specific domains (attention, working memory, memory, executive functioning) suggesting that some individuals may have persistent cognitive symptoms following mTBI (Dean and Sterr, 2013; McInnes et al., 2017). However, a number of other reviews suggest that neuropsychological impairments are not apparent in mTBI, and authors have noted that the high co-occurrence of psychiatric complaints and invalid effort performance may impact testing performance in those with mTBI (Albrecht et al., 2016; Dolan et al., 2012; Frencham et al., 2005; Jak et al., 2015; Rohling et al., 2011; Verfaellie et al., 2014). Data examining the impact of neuropsychological performance on HRQOL and FD in mTBI is limited, but cognitive functioning has been shown to predict worse health outcomes in other mental and physical health conditions (Andreou and Bozikas, 2013; Brissos et al., 2008; Meneses et al., 2009). In one published study, Martindale and colleagues (Martindale et al., 2016) assessed relationships between neuropsychological performance and HRQOL in a veteran sample. The authors found inverse relationships between HRQOL and executive functioning, verbal memory, and motor processing. However, these relationships did not hold when accounting for PTSD and mTBI status

(see also (Disner et al., 2017)). It remains to be established whether neuropsychological variables predict health status outcomes for those with mTBI who perform credibly during testing, and how neuropsychological and health status variables are related in non-veteran samples.

The goals of the current study were two-fold. First, we sought to compare FD and HRQOL ratings among individuals with probable mTBI (with and without PTSD) as compared to healthy comparison participants using a large multi-study repository dataset collected as part of the INjury and TRaUmatic STress (INTRuST) PTSD/TBI Clinical Consortium (W81XWH-08-2-0159). The dataset included participants characterized as having probable mTBI and no PTSD diagnosis (mTBI group) and both probable mTBI and PTSD diagnoses (mTBI/PTSD group), which allowed for examination of group difference on the selected health status outcomes (FD and HRQOL) and relevant neuropsychiatric variables (i.e., mental health symptoms, postconcussive symptoms, neuropsychological performance). Unlike prior studies, these individuals were heterogeneous in terms of civilian, military, or veteran status. Second, we sought to examine associations between ratings of FD and HRQOL and the neuropsychiatric variables within individuals with probable mTBI (irrespective of PTSD status), including mental health symptoms (PTSD, depression, general distress), PCS symptoms, and neuropsychological functioning. To build on prior work, we examined these variables separately to better understand the contribution of each. Consistent with earlier work showing the adverse impact of psychiatric distress on health outcomes (Haagsma, 2015; Jackson et al., 2016), we anticipated that individuals with probable mTBI and PTSD would endorse greater FD and lower HRQOL relative to those without probable mTBI. In line with prior literature (Emanuelson et al., 2003; Haagsma, 2015) we also hypothesized that mental health symptoms, postconcussive symptoms, and neuropsychological functioning would contribute to FD and HRQOL within the patient groups.

2. Methods

2.1 Participants

Participants were 625 individuals in the INTRuST phenotypic data repository which involved completion of questionnaires and provision of a biological sample (data from additional aims of the repository are reported elsewhere). Participants consisted of individuals who enrolled in one of the INTRuST IRB-approved studies and agreed to participate in this supplemental phenotypic repository or individuals recruited specifically for the repository. Participants completed standardized assessments of mental health symptoms, health status outcomes, possible TBI history, and PCS. All measures utilized in the current analyses were collected as part of the baseline or screening visit of the parent trial in which the individual was enrolled, prior to the participant receiving study intervention. Only the 625 individuals who had complete data on health status and symptom variables were included in analyses (out of 702 individuals who completed the study consent). Study participants were divided in three sub-groups: Healthy comparison participants (HC; *n* = 309, neuropsychological data collected for 49.8% (*n* = 156)); mTBI only (*n* = 183, with neuropsychological data for 64.5% (*n* = 120); and mTBI/PTSD (*n* = 133, with neuropsychological data for 61.7% (*n* = 84)).

Inclusion and exclusion criteria were based in part on the individual INTRuST studies in which participants were enrolled (detailed in Supplemental Materials). Specific exclusions for participation in this phenotypic repository in the patient groups were 1) lifetime bipolar I disorder, lifetime psychotic disorders, lifetime dementia, delirium, alcohol or other substance dependence (within 30 days), 2) CNS disorders including aneurysm, anoxic events, brain tumor, encephalitis, Guillain Barre syndrome, Huntington's disease, hydrocephalus, uncontrolled diabetes, thyroid condition or blood pressure, multiple sclerosis, Parkinson's disease, seizure disorder, stroke, or subdural hematoma, 3) currently pregnant or lactating (due to effects of hormonal fluctuations on biological samples collected as part of the repository). For the subgroup of participants who completed a neuroimaging component as part of a separate aim of the repository (*n* = 363) additional exclusion criteria also included: 1) current medications that affect the brain function as determined by the study physician, 2) English as a second

language after the age of 5, 3) history of a learning disability, and 4) weight of more than 300 pounds as this would preclude the subject from entering the scanner.

Each study site recruited healthy comparison participants between the ages of 18 and 65 by using media advertising (Facebook, Craigslist, Yahoo) and registries containing individuals interested in research participation. Responders were briefly screened over the phone for obvious exclusion criteria (e.g., currently taking psychoactive medication, pregnancy). Exclusions for healthy comparison participants included the 1) CNS disorders as described above, 2) medication exclusions, including more than one antihypertensive drug, psychotropic drugs within the last 90 days, herbal psychoactive substance use, or steroid use in the last 4 months, 3) currently pregnant or lactating, 4) history of mood, anxiety, psychotic, dementia, delirium, substance dependence in the past 12 months, 5) history of probable TBI as defined by the I-TBI. Those who initially met inclusion criteria on the phone screen were invited for an in-person qualifying interview (MINI International Neuropsychiatric Interview 6.0.0; MINI (Sheehan et al., 1998)) to ensure that the potential participant qualified as a healthy comparison participant for this study (*n* = 309).

2.2 Measures

2.2.1. TBI History. History of probable TBI was assessed using a self-report questionnaire with items corresponding to the diagnostic criteria of the ACRM (ACRM, 1993). Participants were asked to identify any history of head injury across various categories (e.g., blast, fall). In cases where the individual experienced a head injury, he/she was indicated if they experienced indications of a probable mTBI as a result. Individuals considered positive for probable mTBI endorsed a history of head injury that resulted in one or more of the following: alteration in consciousness (AOC), loss of consciousness (LOC), or posttraumatic amnesia (PTA). The specifier of probable mTBI was created based on duration of AOC/LOC and PTA as per the ACRM guidelines.

2.2.2. Functional disability. Health-related functional disability was assessed using the Sheehan Disability Scale (SDS (Sheehan et al., 1996)). The SDS is a 3-item questionnaire that assesses the extent to which health status impacts activities of daily living, including impairment in work, social, and family domains, which are summed to create a continuous total score ranging from 0 to 30. Higher values indicate a greater level of disability. The measure possesses adequate psychometric properties (Sheehan et al., 1996).

2.2.3. HRQOL. Mental and physical HRQOL were assessed using the Short Form 12-item Health survey (SF-12 (Ware et al., 1996)). The global mental health (MCS-12) and physical health (PCS-12) subscales were calculated with the Quality Metric scoring algorithm. The SF-12 is a shortened version of the Short Form 36 health survey (SF-36), which is a validated measure of HROQOL that evaluates subjective report of the experience of a given problem or condition, and the summary scores selected have demonstrated good validity in contrasting health status across groups (Ware, 2002). The scales range from 0 to 100 with higher ratings indicating better global mental health and global physical health.

2.2.4. PTSD symptoms and diagnostic status. The PTSD Checklist-Civilian Version (PCL-**C** (Weathers et al., 1993)) was administered to assess continuous PTSD symptom severity relative to the individual's worst traumatic experience. The PCL-C is a 17-item measure assessing PTSD symptoms, with items corresponding to diagnostic criteria for PTSD outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). All items are rated on a scale from 1 (*not at all bothersome*) to 5 (*extremely bothersome*) and are totaled by summing symptom severity items (range: 17 to 85). Validation studies indicate that the PCL-C has sound psychometric properties (Weathers et al., 1993). Each participant was assigned a current PTSD diagnosis determined using the procedure of the parent study, which relied on use of a PCL-C cutoff (50) (n = 30) and/or a diagnostic interview using the Clinician Administered PTSD Scale (Blake et al., 1995) (n = 35), or the MINI 6.0.0 (Sheehan et al., 1998) (n = 234).

2.2.5. Depression symptoms. Depression was assessed using the Patient Health Questionnaire-9 (PHQ9 (Kroenke et al., 2001)). The PHQ9 contains 9 items assessing depressive symptoms on a scale from 0 (*not at all*) to 3 (*nearly every* day). Items are summed to create a continuous total severity score, and the scale possesses excellent reliability, criterion validity and construct validity (Kroenke et al., 2001).

2.2.6. General distress symptoms. The Brief Symptom Inventory-18 (BSI-18) Global Severity Index (GSI) was used to assess continuous depression, anxiety, and somatization symptoms. Raw scores were converted to age- and gender-normed T-scores, with T ≥ 63 considered clinical elevation. The BSI-18 has established psychometric properties, including high correspondence with the parent BSI and Symptom Checklist-90-R (Derogatis, 2001).

2.2.7. Postconcussive Symptoms. The Rivermead Post Concussion Symptoms Questionnaire (RPQ (King et al., 1995)) was used to assess PCS in individuals who had experienced probable mTBI. The RPQ contains 16 questions assessing the severity and number of emotional, cognitive, and somatic complaints experienced after head injury. Symptoms were summed within two subscales (RPQ-3 and RPQ-13) based on the recommendations of Eyres and colleagues (Eyres et al., 2005). The RPQ-3 measures headaches, dizziness and nausea, while the RPQ-13 measures remaining emotional (e.g., feeling depressed or tearful), cognitive and somatic symptoms. As part of the questionnaire, participants indicate the presence of symptoms since the identified head injury; however the etiology of symptoms cannot be definitively characterized based on self-report.

2.2.8. Neuropsychological functioning. A subset of individuals (*n* = 360) completed a battery of neuropsychological tests to assess visual and verbal learning and memory (Brief Visuospatial Memory Test-Revised [BVMT-R] total, learning, and long delay recall scores (Benedict, 1997); Rey Auditory Verbal Learning Test -2 [RAVLT-2] total, list B, short and long delay recall scores (Schmidt, 1996; Strauss, 2006)), attention and working memory (Wechsler Memory Scales-III Letter Number Sequencing [WMS-III LNS]

(Wechsler, 1997); Paced Auditory Serial Addition Test [PASAT] number correct (Gronwall, 1977)), psychomotor processing speed (Trail Making Test-A (Reitan, 1993); Wechsler Adult Intelligence Scale-III [WAIS-III] Digit Symbol Coding and Symbol Search (Wechsler, 1997)), executive functioning (Trail Making Test-B (Reitan, 1993)), and academic achievement (Wide Range Achievement Test-4 [WRAT-4] Reading subtest (Wilkinson and Robertson, 2006)). Standardized z, **T**, or scaled scores with demographically corrected norms were calculated for each test using guidelines from the respective administration manuals for all tests, except the PASAT for which a residualized score was calculated using a regression model adjusting for age and education (see Table 2 for a full description of subtests used and normed scores by group). Embedded performance validity metrics were used to evaluate effort and validity during testing, and included the Trail Making Test (total time > 170), BVMT-R (recognition hits < 5), and RAVLT-2 recognition (<10) (Denning, 2012; Shura et al., 2016; Whitney and Davis, 2015). Individuals were required to pass at least two of the three embedded validity measures to be included in the neuropsychological testing analysis ((Larrabee, 2008; Meyers et al., 2014; Meyers and Volbrecht, 2003) in cases where data from one of the validity tests was missing, participants were required to pass all validity tests given; a total of 30 participants failed only on PVT: HC n = 7, mTBI n = 16, mTBI/PTSD n = 7). As a result, n = 15 were removed resulting in a final sample of *n* = 345.

2.3. Statistical analyses

Differences in demographic, health status outcome, mental health symptom, and neuropsychological performance variables across the three groups were analyzed using analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables. Models analyzing symptom variables controlled for age and education. Models analyzing neuropsychological variables controlled for age and gender either by using normed scores or by including the demographic variable as a covariate in the model. Models of neuropsychological variables also controlled for academic achievement to account for the possibility that differences in academic history impacted

scores. Individuals with missing data points for specific neuropsychological tests were excluded listwise (missing data for subtests varied from <1% to 25%). Injury characteristics were collected on a subgroup of participants, and analysis of correlations between injury characteristics and the measured neuropsychiatric variables showed few statistically significant associations (see supplemental materials). Follow-up paired samples were conducted with error rates controlled by Bonferroni correction. Bivariate correlational analyses were conducted to evaluate the associations between each of the neuropsychiatric variables and HRQOL and FD outcomes in the patient groups (those with probable mTBI with or without PTSD).

3. Results

Table 1 presents baseline demographic and clinical characteristics of participants in each group. Individuals in the HC group were significantly younger than individuals in the mTBI and mTBI/PTSD groups, who did not differ from each other. Individuals in the mTBI/PTSD group had significantly fewer years of education than those in the mTBI and HC groups. The mTBI/PTSD and mTBI groups had significantly fewer women than the HC group. For symptoms of PTSD, depression, and general distress, individuals in the mTBI/PTSD group endorsed significantly higher symptoms than those in the mTBI group and the HC group, and individuals in the mTBI group endorsed significantly higher symptoms than those in the HC group. Consistent with our hypotheses, individuals in the mTBI/PTSD group reported significantly lower physical and mental HRQOL, and significantly higher FD than those in the mTBI group and HC group. Individuals in the mTBI group reported significantly lower HRQOL and higher FD than those in the HC group (see Tables 1 and 3; See supplemental materials for results of analyses of symptom outcomes when controlling for general distress). In terms of neuropsychological findings, groups differed on tests of verbal learning and long-delay recall, and tests of psychomotor processing speed (Trails A, Digit Symbol Coding, Symbol Search). Individuals in mTBI/PTSD and mTBI groups

generally attained significantly lower scores than those in the HC group, and the mTBI and mTBI/PTSD groups did not differ statistically from each other (see Tables 2 and 3).

Associations between clinical and demographic variables were evaluated to identify factors related to ratings of health status outcomes in those with probable mTBI, with or without PTSD (Table 4). Age was associated with FD and physical HRQOL, and education was associated with mental HRQOL. All measured mental health symptoms and PCS were associated with FD and HRQOL ratings. Clinical symptoms, including PCS, were also highly inter-correlated. Associations between neuropsychological performance and health outcomes are reported in Table 5. Lower physical HRQOL was associated with lower verbal learning, short-delay verbal memory, visuospatial memory, and the WAIS-III psychomotor processing speed test scores. Higher FD was associated with lower WAIS-III psychomotor processing speed test scores. Lower mental HRQOL was associated with lower Digit Symbol test performance only. Mental health symptoms (BSI, PCL-C, PHQ9) correlated with performance on tests of verbal learning, processing speed, executive functioning, and attention, but not visuospatial performance. Associations between injury characteristics and neuropsychiatric variables, as well as correlations between mental health and PCS symptoms controlling for number of injury events are reported in the supplemental materials).

4. Discussion

mTBI is a relatively common injury that has been previously associated with lower ratings of health status outcomes. The current study examined differences in FD and HRQOL across three groups: healthy comparison participants, individuals with probable mTBI, and individuals with probable mTBI and co-occurring PTSD. Results revealed that individuals with probable mTBI, particularly those with co-occurring PTSD, reported higher FD and lower HRQOL relative to healthy comparison participants. For individuals with probable mTBI (with or without PTSD), all mental health symptoms were strongly correlated with FD and HRQOL. Neuropsychological assessment data in individuals who passed

performance validity tests indicated that aspects of memory and psychomotor processing speed performance were modestly associated with health outcomes in individuals with probable mTBI.

Mental health symptoms of general distress, depression, and PTSD have been linked to self-report of health status in individuals with a history of mTBI in previous studies (Seidl et al., 2015; Steadman-Pare et al., 2001; Williamson et al., 2013). PCS were also associated with lower ratings of FD and physical HRQOL. These data are in line with prior work (Emanuelson et al., 2003; Maguen et al., 2009) suggesting PCS are one factor associated with worse health outcome ratings in individuals with probable mTBI. However, PCS correlated very highly with other mental health symptoms, and controversy exists regarding whether the etiology of PCS relates to general distress rather than to specific mTBI pathophysiology. The etiology of PCS in this sample cannot be conclusively attributed to head injury; rather, other mental and physical health conditions may relate to the PCS individuals reported. Moreover, other symptom self-reports each were highly correlated. This is likely due to multiple factors, including the high co-occurrence of measured mental health symptoms and the overlap in specific symptoms shared across measures. For example, depressive symptoms are assessed as part of the PCS, general distress, and depression-specific questionnaires; similarly irritability is shared across RPQ and PCL-C items. The psychiatric measures were selected to measure distinct constructs (PTSD, depression, anxiety/somatization), but in the current data these variables highly overlapped. As a result, it is not possible to evaluate the specific independent contribution of particular symptom types. The poorer health status outcomes reported in individuals with both probable mTBI and PTSD, as well as the correlation results, are consistent with a cumulative model whereby difficulties with multiple symptom complaints can culminate in exacerbation of disability (Brenner et al., 2009).

In neuropsychological performance domains, performance on verbal learning and memory and processing speed tests differed modestly between groups. While findings of slower speed in the probable mTBI groups than the healthy comparison group are consistent with prior studies, we did not

find evidence for problems with attention or executive functioning (Frencham et al., 2005). We also did not find that individuals with probable mTBI/PTSD differed from those with probable mTBI only in terms of cognitive functioning, although higher attention and executive functioning scores were inversely associated with mental health variables. Thus, subtle cognitive effects were observed in those with probable mTBI, and cognitive performance was not significantly different in probable mTBI alone versus probable mTBI with comorbid PTSD. Within the probable mTBI groups, performance on psychomotor processing speed tests was associated with each of the health outcomes measured, while other cognitive domains showed more specific associations with subtypes of health outcomes (e.g., HRQOL with verbal learning/memory). A growing body of work recognizes the impact of psychomotor speed on daily functioning in other clinical disorders (Multiple Sclerosis (Costa et al., 2016); schizophrenia (Ojeda et al., 2012)). It is possible that slowed processing speed may most directly impact the capacity to complete daily activities, leading to downstream effects such as reduced productivity and efficiency, which impact perceived disability and life satisfaction. Importantly though, the magnitude of observed effects was small and the performance of each group fell within the average range. The clinical significance of group-based neuropsychological differences may thus be small and future research is needed to better understand how cognitive performance ultimately impacts daily activities in individuals with mTBI.

There are a number of limitations to the current study. First, the study is cross-sectional with a diverse group of individuals collected across multiple study sites as part of a consortium. The parent trials of INTRuST included variable inclusion/exclusion criteria, and as such the nature of injury mechanism and associated features likely varied across study (e.g., military blast versus civilian injury). We did not evaluate all injury-related characteristics; participants were no longer in the acute phase of probable mTBI recovery, but the length of time since injury, mechanism of injury, and degree of injury-related symptoms varied across participants and was not comprehensively assessed. Thus, we cannot

determine whether effects were driven by a particular injury type (e.g., blast versus blunt) or whether greater time since injury was associated with fewer symptoms. We also did not assess ongoing litigation. Although there was no obvious secondary gain to biased reporting (research records were not combined with clinical or forensic records) individuals' litigation status may have impacted responding. Though the heterogeneity and size of the sample can be seen as a strength, results are likely not representative of a specific type of mTBI injury or sample (e.g., blast vs. other; military vs. civilian), and the data cannot predict the longitudinal course of health status outcomes over time. The method of injury assessment relied on a relatively brief self-report questionnaire that was based on items used in the VA TBI screener and Brief Traumatic Brain Injury Screen (Donnelly et al., 2011; Schwab et al., 2006) but has not been subject to full psychometric validation. Use of self-report data to evaluate history of mTBI injury is common (Carlson et al., 2011; Hoge et al., 2008), and endorsement of questionnaire items indicating head injury with loss of consciousness, alteration of consciousness, and posttraumatic amnesia have been shown to correspond well to presence of a TBI event using interview-base measures (Lau et al., 2016). However, classification from a brief questionnaire may not fully correspond to data that would have been obtained from multi-source data collection (e.g., interview plus chart review), and this it may be possible that probable mTBI patients were miscategorized in the absence of a corresponding interview-based diagnosis. For example, it is possible that participants endorsed alteration of consciousness that were the result of other etiologies (e.g., extreme stress during trauma), resulting in over-identification of probable mTBI based on this item. Evaluation of mTBI history can be challenging under circumstances where there are no medical records to corroborate injury, but future research would benefit from more detailed evaluation of head injury features. We assessed FD and HRQOL using relatively general metrics, and thus data cannot speak to specific sources of disability (i.e., disability due to one disorder or another). The dataset did not include a comprehensive evaluation of all possible medical and psychiatric conditions of participants. As one example, the presence or absence of ADHD

could impact neuropsychological performance but was not assessed. It will be critical for future research to explore other factors that may relate to HRQOL and FD that may vary across individuals with TBI and/or PTSD, including diagnoses of depression and substance use. We did not include a comprehensive neuropsychological battery (i.e., multiple test in all domains, standalone performance validity measures) to fully characterize neuropsychological profiles. Though measures of performance validity (i.e., credible performance on neuropsychological tests) were included, we did not include metrics of symptom validity (i.e., measure of exaggerated or over-reporting of symptoms; (Larrabee, 2012)). Given that some studies suggest that symptoms may be over-reported in clinical and research settings ((Freeman et al., 2008; Frueh et al., 2000; Tolin et al., 2010) although see (Marx et al., 2008)) it will be important for future research to include measures that capture potential over-endorsement of symptoms.

Taken together, the data underscore the strong association between mental health symptoms and health outcomes in individuals with probable mTBI, and highlight the importance of treating these symptoms. PCS might be an additional intervention target but were very highly correlated with PTSD and other mental health symptoms, consistent with prior data supporting the substantial overlap with PCS and psychiatric distress. A direction for future work will be to explore the effect of psychological, pharmacological, or rehabilitation-focused interventions on broader health outcomes like FD and HRQOL among individuals with mTBI.

References

ACRM, M.T.B.I.C., 1993. Definition of mild traumatic brain injury. Journal of Head Trauma Rehabilitation 8, 86-87.

Ahman, S., Saveman, B.I., Styrke, J., Bjornstig, U., Stalnacke, B.M., 2013. Long-Term Follow-up of Patients with Mild Traumatic Brain Injury: A Mixed-Methods Study. Journal of Rehabilitation Medicine 45 (8), 758-764.

Albrecht, M.A., Masters, C.L., Ames, D., Foster, J.K., 2016. Impact of Mild Head Injury on Neuropsychological Performance in Healthy Older Adults: Longitudinal Assessment in the AIBL Cohort. Front Aging Neurosci 8, 105.

Andreou, C., Bozikas, V.P., 2013. The predictive significance of neurocognitive factors for functional outcome in bipolar disorder. Curr Opin Psychiatry 26 (1), 54-59.

Bazarian, J.J., McClung, J., Shah, M.N., Cheng, Y.T., Flesher, W., Kraus, J., 2005. Mild traumatic brain injury in the United States, 1998--2000. Brain Inj 19 (2), 85-91.

Belanger, H.G., Kretzmer, T., Vanderploeg, R.D., French, L.M., 2010. Symptom complaints following combat-related traumatic brain injury: relationship to traumatic brain injury severity and posttraumatic stress disorder. J Int Neuropsychol Soc 16 (1), 194-199.

Benedict, R.H., 1997. Brief Bisuospatial Memory Test-Revised. Psychological Assessment Resources, Inc., Odessa, FL.

Beseoglu, K., Roussaint, N., Steiger, H.J., Hanggi, D., 2013. Quality of life and socio-professional reintegration after mild traumatic brain injury. Br J Neurosurg 27 (2), 202-206.

Blake, D.D., Weathers, F.W., Nagy, L.M., Kaloupek, D.G., Gusman, F.D., Charney, D.S., Keane, T.M., 1995. The development of a Clinician-Administered PTSD Scale. Journal of Traumatic Stress 8 (1), 75-90.

Boyle, E., Cancelliere, C., Hartvigsen, J., Carroll, L.J., Holm, L.W., Cassidy, J.D., 2014. Systematic review of prognosis after mild traumatic brain injury in the military: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil 95 (3 Suppl), S230-237.

Brenner, L.A., Vanderploeg, R.D., Terrio, H., 2009. Assessment and diagnosis of mild traumatic brain injury, posttraumatic stress disorder, and other polytrauma conditions: burden of adversity hypothesis. Rehabil Psychol 54 (3), 239-246.

Brissos, S., Dias, V.V., Kapczinski, F., 2008. Cognitive performance and quality of life in bipolar disorder. Can J Psychiatry 53 (8), 517-524.

Broshek, D.K., De Marco, A.P., Freeman, J.R., 2015. A review of post-concussion syndrome and psychological factors associated with concussion. Brain Inj 29 (2), 228-237.

Bryant, R.A., O'Donnell, M.L., Creamer, M., McFarlane, A.C., Clark, C.R., Silove, D., 2010. The psychiatric sequelae of traumatic injury. Am J Psychiatry 167 (3), 312-320.

Carlson, K.F., Kehle, S.M., Meis, L.A., Greer, N., Macdonald, R., Rutks, I., Sayer, N.A., Dobscha, S.K., Wilt, T.J., 2011. Prevalence, assessment, and treatment of mild traumatic brain injury and posttraumatic stress disorder: a systematic review of the evidence. J Head Trauma Rehabil 26 (2), 103-115.

Cassidy, J.D., Cancelliere, C., Carroll, L.J., Cote, P., Hincapie, C.A., Holm, L.W., Hartvigsen, J., Donovan, J., Nygren-de Boussard, C., Kristman, V.L., Borg, J., 2014. Systematic review of self-reported prognosis in adults after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil 95 (3 Suppl), S132-151.

Costa, S.L., Genova, H.M., DeLuca, J., Chiaravalloti, N.D., 2016. Information processing speed in multiple sclerosis: Past, present, and future. Multiple Sclerosis.

Dean, P.J., Sterr, A., 2013. Long-term effects of mild traumatic brain injury on cognitive performance. Front Hum Neurosci 7, 30.

Denning, J.H., 2012. The efficiency and accuracy of the Test of Memory Malingering trial 1, errors on the first 10 items of the test of memory malingering, and five embedded measures in predicting invalid test performance. Arch Clin Neuropsychol 27 (4), 417-432.

Derogatis, L.R., 2001. Brief Symptom Inventory 18. Pearson, Inc., Minneapolis, MN.

Dijkers, M.P., 2004. Quality of life after traumatic brain injury: A review of research approaches and findings. Arch Phys Med Rehabil 85 (4), S21-S35.

Disner, S.G., Kramer, M.D., Nelson, N.W., Lipinski, A.J., Christensen, J.M., Polusny, M.A., Sponheim, S.R., 2017. Predictors of Postdeployment Functioning in Combat-Exposed U.S. Military Veterans. Clinical Psychological Science in press.

Dolan, S., Martindale, S., Robinson, J., Kimbrel, N.A., Meyer, E.C., Kruse, M.I., Morissette, S.B., Young, K.A., Gulliver, S.B., 2012. Neuropsychological sequelae of PTSD and TBI following war deployment among OEF/OIF veterans. Neuropsychol Rev 22 (1), 21-34.

Donnell, A.J., Kim, M.S., Silva, M.A., Vanderploeg, R.D., 2012. Incidence of postconcussion symptoms in psychiatric diagnostic groups, mild traumatic brain injury, and comorbid conditions. Clin Neuropsychol 26 (7), 1092-1101.

Donnelly, K.T., Donnelly, J.P., Dunnam, M., Warner, G.C., Kittleson, C.J., Constance, J.E., Bradshaw, C.B., Alt, M., 2011. Reliability, sensitivity, and specificity of the VA traumatic brain injury screening tool. J Head Trauma Rehabil 26 (6), 439-453.

Emanuelson, I., Andersson Holmkvist, E., Bjorklund, R., Stalhammar, D., 2003. Quality of life and post-concussion symptoms in adults after mild traumatic brain injury: a population-based study in western Sweden. Acta Neurol Scand 108 (5), 332-338.

Eyres, S., Carey, A., Gilworth, G., Neumann, V., Tennant, A., 2005. Construct validity and reliability of the Rivermead Post-Concussion Symptoms Questionnaire. Clin Rehabil 19 (8), 878-887.

Faul, M., Xu, L., Wald, M. M., Coronado, V. G. , 2010. Traumatic brain injury in the United States: emergency department visits, hospitilizations, and deaths. . Centesr for Disease Control and Prevention, National Center for Injury Prevention and Control, Atlanta, GA.

Freeman, T., Powell, M., Kimbrell, T., 2008. Measuring symptom exaggeration in veterans with chronic posttraumatic stress disorder. Psychiatry Research 158 (3), 374-380.

Frencham, K.A., Fox, A.M., Maybery, M.T., 2005. Neuropsychological studies of mild traumatic brain injury: a meta-analytic review of research since 1995. J Clin Exp Neuropsychol 27 (3), 334-351.

Frueh, B.C., Hamner, M.B., Cahill, S.P., Gold, P.B., Hamlin, K.L., 2000. Apparent symptom overreporting in combat veterans evaluated for PTSD. Clin Psychol Rev 20 (7), 853-885.

Gronwall, D.M., 1977. Paced auditory serial-addition task: a measure of recovery from concussion. Percept Mot Skills 44 (2), 367-373.

Haagsma, J.A., Scholten, C., Andriessen, T. M. J.C., Vos, P. E., Van Beeck, E. F., Polinder, S., 2015. Impact of depression and posttraumatic stress disorder on functional outcome and health-related quality of life of patients with mild traumatic brain injury. J Neurotrauma 32, 853-962.

Hoge, C.W., Engel, C.C., Castro, C.A., 2008. Mild traumatic brain injury in US soldiers returning from Iraq - Reply. New England Journal of Medicine 358 (20), 2179-2179.

Hoge, C.W., Goldberg, H.M., Castro, C.A., 2009. Care of war veterans with mild traumatic brain injury--flawed perspectives. N Engl J Med 360 (16), 1588-1591.

Jackson, C.E., Green, J.D., Bovin, M.J., Vasterling, J.J., Holowka, D.W., Ranganathan, G., Rosen, R.C., Keane, T.M., Marx, B.P., 2016. Mild Traumatic Brain Injury, PTSD, and Psychosocial Functioning Among Male and Female U.S. OEF/OIF Veterans. Journal of Traumatic Stress 29 (4), 309-316.

Jak, A.J., Gregory, A., Orff, H.J., Colon, C., Steele, N., Schiehser, D.M., Delano-Wood, L., Jurick, S.M., Twamley, E.W., 2015. Neuropsychological performance in treatment-seeking Operation

Enduring Freedom/Operation Iraqi Freedom Veterans with a history of mild traumatic brain injury. J Clin Exp Neuropsychol 37 (4), 379-388.

Kay, T., Newman, B., Cavallo, M., Ezrachi, O., Resnick, M., 1992. Toward a neuropsychological model of disability after mild traumatic brain injury. Neuropsychology 6 (4), 371-384.

King, N.S., Crawford, S., Wenden, F.J., Moss, N.E., Wade, D.T., 1995. The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. J Neurol 242 (9), 587-592.

Kroenke, K., Spitzer, R.L., Williams, J.B., 2001. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 16 (9), 606-613.

Kuyken, W., Orley, J., Power, M., Herrman, H., Schofield, H., Murphy, B., Metelko, Z., Szabo, S., Pibernikokanovic, M., Quemada, N., Caria, A., Rajkumar, S., Kumar, S., Saxena, S., Baron, D., Amir, M., Tazaki, M., Noji, A., Vanheck, G., Devries, J., Sucre, J.A., Picardami, L., Kabanov, M., Lomachenkov, A., Burkovsky, G., Carrasco, R.L., Bodharamik, Y., Meesapya, K., Skevington, S., Patrick, D., Martin, M., Wild, D., Acuda, W., Mutambirwa, J., Aaronson, N.K., Bech, P., Bullinger, M., Chen, H.N., Foxrushby, J., Moinpour, C., Rosser, R., Buesching, D., Bucquet, D., Chambers, L.W., Jambon, B., Jenkins, C.D., Deleo, D., Fallowfield, L., Gerin, P., Graham, P., Gureje, O., Kalumba, K., Kerrcorrea, Mercier, C., Oliver, J., Poortinga, Y.H., Trotter, R., Vandam, F., 1995. The World-Health-Organization Quality-of-Life Assessment (Whoqol) - Position Paper from the World-Health-Organization. Social science & medicine 41 (10), 1403-1409.

Lagarde, E., Salmi, L.R., Holm, L.W., Contrand, B., Masson, F., Ribereau-Gayon, R., Laborey, M., Cassidy, J.D., 2014. Association of symptoms following mild traumatic brain injury with posttraumatic stress disorder vs. postconcussion syndrome. JAMA Psychiatry 71 (9), 1032-1040.

Larrabee, G.J., 2008. Aggregation across multiple indicators improves the detection of malingering: relationship to likelihood ratios. Clin Neuropsychol 22 (4), 666-679.

Larrabee, G.J., 2012. Performance validity and symptom validity in neuropsychological assessment. J Int Neuropsychol Soc 18 (4), 625-630.

Lau, K.M., Madden, E., Neylan, T.C., Seal, K.H., Maguen, S., 2016. Assessing for mild TBI among Iraq and Afghanistan veterans: Outcomes of injury severity and neurological factors. Brain Inj 30 (3), 287-294.

Maguen, S., Stalnaker, M., McCaslin, S., Litz, B.T., 2009. PTSD subclusters and functional impairment in Kosovo peacekeepers. Mil Med 174 (8), 779-785.

Martindale, S.L., Morissette, S.B., Kimbrel, N.A., Meyer, E.C., Kruse, M.I., Gulliver, S.B., Dolan, S.L., 2016. Neuropsychological functioning, coping, and quality of life among returning war veterans. Rehabil Psychol 61 (3), 231-239.

Marx, B.P., Miller, M.W., Sloan, D.M., Litz, B.T., Kaloupek, D.G., Keane, T.M., 2008. Military-related PTSD, current disability policies, and malingering. American journal of public health 98 (5), 773-774.

McInnes, K., Friesen, C.L., MacKenzie, D.E., Westwood, D.A., Boe, S.G., 2017. Mild Traumatic Brain Injury (mTBI) and chronic cognitive impairment: A scoping review. PLoS One 12 (4), e0174847.

McMahon, P., Hricik, A., Yue, J.K., Puccio, A.M., Inoue, T., Lingsma, H.F., Beers, S.R., Gordon, W.A., Valadka, A.B., Manley, G.T., Okonkwo, D.O., Investigators, T.-T., 2014. Symptomatology and functional outcome in mild traumatic brain injury: results from the prospective TRACK-TBI study. J Neurotrauma 31 (1), 26-33.

Meneses, R.F., Pais-Ribeiro, J.L., da Silva, A.M., Giovagnoli, A.R., 2009. Neuropsychological predictors of quality of life in focal epilepsy. Seizure 18 (5), 313-319.

Meyers, J.E., Miller, R.M., Thompson, L.M., Scalese, A.M., Allred, B.C., Rupp, Z.W., Dupaix, Z.P., Junghyun Lee, A., 2014. Using likelihood ratios to detect invalid performance with performance validity measures. Arch Clin Neuropsychol 29 (3), 224-235.

Meyers, J.E., Volbrecht, M.E., 2003. A validation of multiple malingering detection methods in a large clinical sample. Arch Clin Neuropsychol 18 (3), 261-276.

Nichol, A.D., Higgins, A.M., Gabbe, B.J., Murray, L.J., Cooper, D.J., Cameron, P.A., 2011. Measuring functional and quality of life outcomes following major head injury: Common scales and checklists. Injury-International Journal of the Care of the Injured 42 (3), 281-287.

O'Neil, M.E., Callahan, M., Carlson, K.F., Roost, M., Laman-Maharg, B., Twamley, E.W., Iverson, G.L., Storzbach, D., 2017. Postconcussion symptoms reported by Operation Enduring Freedom/Operation Iraqi Freedom veterans with and without blast exposure, mild traumatic brain injury, and posttraumatic stress disorder. J Clin Exp Neuropsychol 39 (5), 449-458.

Ojeda, N., Sanchez, P., Pena, J., Elizagarate, E., Yoller, A.B., Gutierrez-Fraile, M., Ezcurra, J., Napal, O., 2012. An explanatory model of quality of life in schizophrenia: the role of processing speed and negative symptoms. Actas Esp Psiquiatr 40 (1), 10-18.

Petchprapai, N., Winkelman, C., 2007. Mild traumatic brain injury: determinants and subsequent quality of life. A review of the literature. J Neurosci Nurs 39 (5), 260-272.

Polinder, S., Haagsma, J.A., van Klaveren, D., Steyerberg, E.W., van Beeck, E.F., 2015. Health-related quality of life after TBI: a systematic review of study design, instruments, measurement properties, and outcome. Popul Health Metr 13, 4.

Reitan, R.M., Wolfson, D., 1993. The Halstead-Reitan neuropsychological test battery: Theoretical and clinical interpretation. Neuropsychology Press, Tucson, AZ.

Rohling, M.L., Binder, L.M., Demakis, G.J., Larrabee, G.J., Ploetz, D.M., Langhinrichsen-Rohling, J., 2011. A meta-analysis of neuropsychological outcome after mild traumatic brain injury: re-analyses and reconsiderations of Binder et al. (1997), Frencham et al. (2005), and Pertab et al. (2009). Clin Neuropsychol 25 (4), 608-623.

Schiehser, D.M., Twamley, E.W., Liu, L., Matevosyan, A., Filoteo, J.V., Jak, A.J., Orff, H.J., Hanson, K.L., Sorg, S.F., Delano-Wood, L., 2015. The Relationship Between Postconcussive Symptoms and Quality of Life in Veterans With Mild to Moderate Traumatic Brain Injury. J Head Trauma Rehabil 30 (4), E21-28.

Schmidt, M., 1996. Rey Auditory and Verbal Learning Test: A handbook. Western Psychological Services, Los Angeles, CA.

Scholten, A.C., Haagsma, J.A., Andriessen, T.M.J.C., Vos, P.E., Steyerberg, E.W., van Beeck, E.F., Polinder, S., 2015. Health-related quality of life after mild, moderate and severe traumatic brain injury: Patterns and predictors of suboptimal functioning during the first year after injury. Injury-International Journal of the Care of the Injured 46 (4), 616-624.

Schwab, K.A., Baker, G., Ivins, B.J., Sluss-Tiller, M., Lux, W., Warden, D., 2006. The Brief Traumatic Brain Injury Screen (BTBIS): Investigating the validity of a self-report instrument for detecting traumatic brain injury (TBI) in troops returning from deployment in Afghanistan and Iraq. Neurology 66 (5), A235-A235.

Seidl, J.N.T., Pastorek, N.J., Lillie, R., Rosenblatt, A., Troyanskaya, M., Miller, B.I., Romesser, J., Lippa, S., Sim, A.H., Linck, J., 2015. Factors Related to Satisfaction With Life in Veterans With Mild Traumatic Brain Injury. Rehabil Psychol 60 (4), 335-343.

Sheehan, D.V., Harnett-Sheehan, K., Raj, B.A., 1996. The measurement of disability. Int Clin Psychopharmacol 11 Suppl 3, 89-95.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59 Suppl 20, 22-33;quiz 34-57.

Shura, R.D., Miskey, H.M., Rowland, J.A., Yoash-Gantz, R.E., Denning, J.H., 2016. Embedded Performance Validity Measures with Postdeployment Veterans: Cross-Validation and Efficiency with Multiple Measures. Appl Neuropsychol Adult 23 (2), 94-104.

Silverberg, N.D., Iverson, G.L., 2011. Etiology of the post-concussion syndrome: Physiogenesis and Psychogenesis revisited. Neurorehabilitation 29 (4), 317-329.

Steadman-Pare, D., Colantonio, A., Ratcliff, G., Chase, S., Vernich, L., 2001. Factors associated with perceived quality of life many years after traumatic brain injury. Journal of Head Trauma Rehabilitation 16 (4), 330-342.

Stein, M.B., Ursano, R.J., Campbell-Sills, L., Colpe, L.J., Fullerton, C.S., Heeringa, S.G., Nock, M.K., Sampson, N.A., Schoenbaum, M., Sun, X., Jain, S., Kessler, R.C., 2016. Prognostic Indicators of Persistent Post-Concussive Symptoms after Deployment-Related Mild Traumatic Brain Injury: A Prospective Longitudinal Study in U.S. Army Soldiers. J Neurotrauma 33 (23), 2125-2132.

Strauss, E., Sherman, E.M.S., Spreen, O., 2006. A compendium of Neuropsychological Tests: Administration, Norms, and Commentary, 3 ed. Oxford University Press, New York, NY.

Tolin, D.F., Steenkamp, M.M., Marx, B.P., Litz, B.T., 2010. Detecting Symptom Exaggeration in Combat Veterans Using the MMPI-2 Symptom Validity Scales: A Mixed Group Validation. Psychol Assess 22 (4), 729-736.

Vasterling, J.J., Aslan, M., Lee, L.O., Proctor, S.P., Ko, J., Jacob, S., Concato, J., 2017. Longitudinal Associations among Posttraumatic Stress Disorder Symptoms, Traumatic Brain Injury, and Neurocognitive Functioning in Army Soldiers Deployed to the Iraq War. Journal of the International Neuropsychological Society 1 (13).

Verfaellie, M., Lafleche, G., Spiro, A., Bousquet, K., 2014. Neuropsychological outcomes in OEF/OIF veterans with self-report of blast exposure: associations with mental health, but not MTBI. Neuropsychology 28 (3), 337-346.

Ware, J., Jr., Kosinski, M., Keller, S.D., 1996. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 34 (3), 220-233.

Ware, J.E., Kosinski, M., Turner-Bowker, D. M., Gandek, B., 2002. How to Score Version 2 of the SF-12® Health Survey (With a Supplement Documenting Version 1) Quality Metric Incorporated, Lincoln, RI.

Weathers, F.W., Litz, B.T., Herman, D.S., Huska, J.A., Keane, T.M., 1993. The PTSD checklist

(PCL): Reliability, validity, and diagnostic utility, Annual Conference of the International Society for Traumatic Stress Studies, San Antonio, TX.

Wechsler, D., 1997. Wechsler Adult Intelligence Scale-third edition: Adminsitration and Scoring manual. Psychological Corporation, San Antonio, TX.

Whiteneck, G.G., Cuthbert, J.P., Corrigan, J.D., Bogner, J.A., 2016. Prevalence of Self-Reported Lifetime History of Traumatic Brain Injury and Associated Disability: A Statewide Population-Based Survey. Journal of Head Trauma Rehabilitation 31 (1), E55-E62.

Whitney, K.A., Davis, J.J., 2015. The non-credible score of the Rey Auditory Verbal Learning Test: is it better at predicting non-credible neuropsychological test performance than the RAVLT recognition score? Arch Clin Neuropsychol 30 (2), 130-138.

Wilkinson, G.S., Robertson, G.J., 2006. Wide Range Achievement test4 professional manual. Psychological Assessment Resources, Lutz, FL.

Williamson, M.L.C., Elliott, T.R., Berry, J.W., Underhill, A.T., Stavrinos, D., Fine, P.R., 2013. Predictors of health-related quality-of-life following traumatic brain injury. Brain Inj 27 (9), 992-999.

Acknowledgement

This work was supported by the CDRP award W81XWH-08-2-0159 (Stein et al) and the VA Office of Academic Affairs and CSR&D (J. Bomyea CX001600-01A1). Thank you to Charles Kim for his assistance with the preparation of this manuscript.

Table 1
Baseline demographic variables and clinical characteristics by group

	HC (*n* = 309)	mTBI only (*n* = 183)	mTBI/PTSD (*n* = 133)	Skewness	Kurtosis
N Race					
White	209	147	91		
Black or African American	55	22	27		
Asian	24	2	1		
Native Hawaiian; Pacific Islander	1	1	1		
Native American ; Alaska Native	0	1	1		
Other or unknown	20	10	12		
N Gender***					
Female	155	60	20		
Male	153	122	111		
Mean Age***	32.0 (11.6)	36.0 (12.2)	38.0 (10.1)	0.63	-0.67
Mean Years Education***	15.3 (2.7)	14.6 (2.7)	13.8 (2.1)	<0.01	3.21
Mean PCL-**C****	19.2 (4.7)	26.1 (9.2)	59.0 (12.3)	1.34	0.52
Mean PHQ9***	0.9 (1.5)	3.8 (4.1)	13.0 (5.8)	1.53	1.41
Mean BSI***	19.8 (3.0)	24.1 (7.4)	43.6 (13.8)	1.94	3.35
Mean SDS***	0.3 (1.3)	6.3 (8.2)	17.8 (7.6)	1.32	0.34
Mean SF12-MCS***	55.3 (5.0)	50.6 (8.9)	33.0 (10.2)	-1.13	0.39
Mean SF12-PCS***	55.5 (3.7)	50.0 (10.0)	44.4 (11.1)	-1.54	1.86
Mean RPQ-3***		1.5 (2.6)	4.0 (3.1)	1.02	0.08
Mean RPQ-13***		8.8 (11.2)	29.7 (13.0)	0.32	-1.32
Estimated years since probable mTBIł		**9.09 (10.78)**	**9.08 (9.90)**		
Self reported number of probable mTBIsł		**2.20 (3.17)**	**3.38 (3.36)**		
N presence of LOCł					
No		**37**	**24**		
Yes		**108**	**69**		

Note: **HC = healthy comparison participants, mTBI = participants with probable mild TBI; mTBI/PTSD = = participants with probable mild TBI and posttraumatic stress disorder;** PCL-**C** = PTSD Checklist **civilian version**; PHQ9 = Patient Health Questionnaire-9; BSI = Brief Symptom Inventory; SDS = Sheehan Disability Scale; SF12-MCS = Mental Health quality of life; SF12-PCS = Physical health quality of life, ; RPQ-3 = 3-item subscale of the Rivermead Postconcussive Symptoms Questionnaire; RPQ-13 = 13-item subscale of the Rivermead Postconcussion Symptoms Questionnaire. Omnibus effect controlling for age and gender *** $p < 0.001$. **ł Injury characteristics were based on a subsample with these available data, n = 107, 165, and 238 respectively.**

Table 2

Neuropsychological performance by group

	HC (*n* = 152)	mTBI only (*n* = 116)	mTBI/PTSD (*n* = 77)	Skewness	Kurtosis	Effect size $_p\eta^2$
WRAT-**4** score	64.00 (4.76)	64.35 (4.26)	63.30 (4.47)	-1.32	2.68	0 .01
RAVLT-**2** z score						
Total***	0.45 (1.11)	0.00 (1.22)	-0.18 (0.91)	-0.39	0.39	0.06
List B***	0.32 (1.14)	-0.11 (0.98)	-0.21 (0.90)	0.58	0.85	0.05
Short delay recall	0.26 (1.04)	0.02 (1.39)	0.00 (0.96)	-1.06	2.00	0.01
Long delay recall**	0.26 (1.01)	-0.12 (1.25)	-0.15 (1.01)	-0.88	0.80	0.03
BVMT-**R** t score						
Total	52.91 (10.46)	50.13 (11.54)	50.25 (11.33)	-0.58	-0.18	0.01
Learning	49.41 (11.22)	50.49 (10.82)	51.41 (11.48)	0.08	-0.58	0.01
Long delay recall	52.73 (9.90)	50.59 (11.74)	52.37 (10.95)	-1.22	0.79	0.01
Trail Making Test t score						
Trails A*	53.78 (10.93)	49.29 (11.97)	50.51 (13.75)	0.06	-0.19	0.03
Trails B	56.06 (11.4)	53.35 (11.35)	53.79 (13.03)	0.06	-0.21	0.01
WMS-III scaled score						
L-N Sequencing	11.82 (2.93)	11.40 (2.76)	11.13 (2.84)	0.18	0.36	0.01
WAIS-III scaled score						
D-S Coding***	11.39 (3.12)	9.83 (2.62)	9.06 (2.49)	0.26	-0.34	0.09
S-Search*	12.21 (2.68)	11.51 (2.57)	11.13 (3.03)	0.13	0.37	0.02
PASAT z score	-0.06 (1.10)	0.09 (0.90)	0.21 (0.90)	-0.66	-0.21	0.01

Note: Individuals who did not pass embedded performance validity measures not included in table 2. HC = healthy comparison participants, mTBI = participants with probable mild TBI; mTBI/PTSD = participants with probable mild TBI and posttraumatic stress disorder. RAVLT-**2** = Rey Auditory Learning Test-**2**; BVMT-**R** = Brief Visuospatial Memory Test-**Revised**; Trails = Trail Making Test; WMS-**III** = Wechsler Memory Scales-**III**; L-N Sequencing = Letter-Number Sequencing; WAIS-**III** = Wechsler Adult Intelligence Scales-III; D-S Coding = Digit-Symbol Coding; S-Search = Symbol Search; PASAT = paced Auditory Serial Addition Test. N included in each subtest varied based on missing data (n range 297-353). See table 3 for pairwise comparisons with confidence intervals. Omnibus effects *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Table 3

Pairwise comparisons on demographic, clinical, and neuropsychological characteristics

	HC vs. mTBI; 95% CI, *p*-value	HC vs. mTBI/PTSD; 95% CI, *p*-value	mTBI vs. mTBI/PTSD; 95% CI, *p*-value
Age	[-6.63, -1.39], 0.001*	[-8.85, -2.87], <0.001*	[-5.03, 1.33], ns
Education	[-0.01, 1.19], ns*	[0.76, 2.15], <0.001*	[0.13, 1.59], 0.01*
PCL-**C**	[-8.37 -4.54], <0.001*	[-41.29, -36.88], <0.001*	[-34.94, -30.32], <0.001*
PHQ9	[-3.60, -1.95], <0.001*	[-13.01, -11.11], <0.001*	[-10.28, -8.29], <0.001*
BSI	[-6.14, -2.51], <0.001*	[-25.92, -21.73], <0.001*	[-21.69, -17.31], <0.001*
SDS	[-7.13, -4.51], <0.001*	[-18.92, -15.91], <0.001*	[-13.17, -10.02], <0.001*
SF12-PCS	[2.98, 6.55], <0.001*	[8.03, 12.14], <0.001*	[3.17, 7.47], <0.001*
SF12-MCS	[2.94, 6.41], <0.001*	[20.39, 24.38], <0.001*	[15.62, 19.80], <0.001*
RAVLT-**2**			
Total	[0.14, 0.80], 0.002*	[0.21, 0.96], 0.001*	[-0.28, 0.51], ns
List B	[0.13, 0.74], 0.002*	[0.16, 0.85], 0.002*	[-0.30, 0.44], ns
Long delay recall	[0.08, 0.73], 0.01*	[0.01, 0.76], 0.04*	[-0.42, 0.37], ns
Trails A	[0.74, 8.13], 0.01*	[-1.35, 7.54], ns	[-5.85, 3.187], ns
WAIS-III			
D-S Coding	[0.74, 2.40], <0.001*	[1.00, 2.96] <0.001*	[-0.61, 1.43], ns
S-Search	[-0.07, 1.55], ns	[0.003, 1.92], ns	[-0.77, 1.21], ns

Note: HC = healthy comparison participants, mTBI = participants with probable mild TBI; mTBI/PTSD = participants with probable mild TBI and posttraumatic stress disorder; PCL-**C** = PTSD Checklist **civilian version**; PHQ9 = Patient Health Questionnaire; BSI = Brief Symptom Inventory; SDS = Sheehan Disability Scale; SF12-MCS = Mental Health quality of life; SF12-PCS = Physical health quality of life; RAVLT-**2** = Rey Auditory Learning Test-**2;** WAIS-**III** = Wechsler Adult Intelligence Scales-**III**; D-S Coding = Digit-Symbol Coding; S-Search = Symbol Search. Only includes participants who passed PVT measures. * = survives FDR correction at $p < 0.05$.

Table 4

*Correlations between demographic variables, clinical characteristics, and FD and QOL in participants with **probable** mTBI **and probable mTBI and PTSD***

Variable	1	2	3	4	5	6	7	8	9	10	11
1. SDS	1										
2. SF12-PCS	-0.54***	1									
3. SF12-MCS	-0.68***	0.12*	1								
4. Age	0.18**	-0.21***	-0.08	1							
5. Education	-0.05	0.05	0.12*	0.12*	1						
6. Gender	-0.03	0.07	0.10	-0.02	0.17**	1					
7. PCL-**C**	0.70***	-0.34***	-0.75***	0.15**	-0.14*	-0.21***	1				
8. PHQ9	0.76***	-0.43***	-0.82***	0.09	-0.15**	-0.09	0.78***	1			
9. BSI	0.70***	-0.35***	-0.76***	0.09	-0.12*	-0.10	0.80***	0.84***	1		
10. RPQ-3	0.57***	-0.47***	-0.42***	0.09	-0.06	0.06	0.51***	0.57***	0.54***	1	
11. RPQ-13	0.73***	-0.48***	-0.65***	0.16**	-0.14*	-0.14*	0.79***	0.79***	0.72***	0.70***	1

Note: PCL-**C** = PTSD Checklist **civilian version**; PHQ9 = Patient Health Questionnaire; BSI = Brief Symptom Inventory; SDS = Sheehan Disability Scale; SF12-MCS = Mental Health quality of life; SF12-PCS = Physical health quality of life; RPQ-3 = 3-item subscale of the Rivermead Postconcussive Symptoms Questionnaire; RPQ-13 = 13-item subscale of the Rivermead Postconcussion Symptoms Questionnaire. ***p< 0.001, **p< 0.01, *p< 0.05.

Table 5.

Correlations with health outcomes, symptoms, and cognitive performance in individuals ***with neuropsychological testing data in the probable mTBI or probable mTBI and PTSD groups***

	RAVLT-**2** Total	RAVLT-**2** List B	RAVLT-**2** Short recall	RAVLT-**2** Long recall	BVMT-**R** Total	BVMT-**R** Learning	BVMT-**R** Long recall	Trail Making Test A	Trail Making Test B	WMS-III L-N Seq	WAIS-III D-S Coding	WAIS-III S- Search	PASAT
SDS	-0.11	-0.07	-0.11	-0.05	-0.06	0.04	-0.12	-0.09	-0.08	0.004	-0.27***	-0.17*	-0.07
SF12-PCS	0.16*	-0.02	-0.16*	0.13	0.04	-0.02	0.19*	0.10	0.07	0.08	0.20**	0.22**	0.12
SF12-MCS	0.04	0.04	0.01	-0.02	0.01	-0.01	-0.002	0.04	0.10	-0.01	0.20**	0.08	0.03
PCL-**C**	-0.12	-0.09	-0.07	-0.10	-0.03	-0.001	-0.002	0.02	-0.06	-0.07	-0.23**	-0.12	-0.06
PHQ9	-0.12	-0.10	-0.12	-0.09	-0.13	0.03	-0.15	-0.08	-0.18**	-0.07	-0.20**	-0.14	-0.15*
BSI	-0.12	-0.08	-0.08	-0.04	-0.09	0.03	-0.13	-0.07	-0.12	-0.07	-0.18**	-0.12	-0.13
RPQ-3	-0.17*	-0.14	-0.08	-0.11	0.01	0.05	-0.02	-0.04	-0.04	-0.02	-0.09	-0.02	-0.14
RPQ-13	-0.15	-0.11	-0.11	-0.09	-0.08	0.03	-0.04	-0.05	-0.11	-0.07	-0.24**	-0.15*	-0.10

Note: PCL-**C** = PTSD Checklist **civilian version**; PHQ9 = Patient Health Questionnaire; BSI = Brief Symptom Inventory; SDS = Sheehan Disability Scale; SF12-MCS = Mental Health quality of life; SF12-PCS = Physical health quality of life, ; RPQ-3 = 3-item subscale of the Rivermead Postconcussive Symptoms Questionnaire; RPQ-13 = 13-item subscale of the Rivermead Postconcussion Symptoms Questionnaire; RAVLT-**2** = Rey Auditory Learning Test-**2**; BVMT-**R** = Brief Visuospatial Memory Test-**Revised**; Trails = Trail Making Test; WMS-**III** = Wechsler Memory Scales-**III**; L-N Sequencing = Letter-Number Sequencing; WAIS-III = Wechsler Adult Intelligence Scales-III; D-S Coding = Digit-Symbol Coding; S-Search = Symbol Search PASAT = Paced Auditory Serial Addition Test. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.